



CASE: LA0112 NP

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Burton Rodney
Type or print name

Signature

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

ART UNIT: 1626

TIMUR GUNGOR, ET AL.

EXAMINER: STOCKTON, LAURA LYNNE

APPLICATION NO: 10/775,742

FILED: 02/10/2004

FOR: NOVEL THIAZOLIDINE COMPOUNDS AS CALCIUM
SENSING RECEPTOR MODULATORS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF PRIOR INVENTION OF TIMUR GUNGOR AND
JOHN K. DICKSON, JR. TO OVERCOME CITED U.S. PATENT NO. 6,673,821

To the Commissioner for Patents and Trademarks:

1. This Declaration is to establish reduction to practice of the invention in this application at a date prior to October 22, 2001, that is the filing date of U.S. application Serial No. 10/007,342, now U.S. Patent No. 6,673,821 to Wang et al.
2. Timur Gungor and John K. Dickson, Jr. declare as follows.
3. That at the time of the conception and reduction to practice of the invention in the subject application, they each had a Ph. D in Organic Chemistry and were employed as chemists by Bristol-Myers Squibb Company, the assignee of the subject application as evidenced by an

assignment signed by each and recorded at the U.S. Patent and Trademark Office on July 13, 2004, Reel 014844, Frame 0440 (ATTACHMENT I).

4. That they are the inventors of the invention claimed in U.S. patent application Serial No. 10/775,742 filed February 10, 2004.

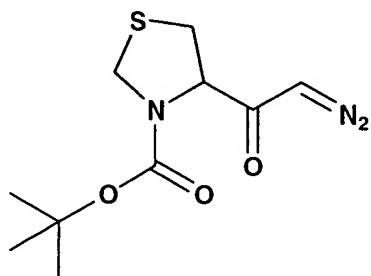
5. That the invention defined in the claims as filed was conceived and reduced to practice in the United States prior to October 22, 2001.

6. That prior to October 22, 2001, Timur Gungor and John K. Dickson, Jr. conceived of a genus of compounds covered by the claims of the subject application and which includes the compound selected for prosecution in the subject application, that is, the compound prepared in Example 1 of such application (also identified as BMS 515,832), which conception was recorded by Timur Gungor as CaR Program TG Propositions each dated prior to October 22, 2001 and CaR Target, copies of which are attached hereto and identified as ATTACHMENTS A and B, respectively.

7. That prior to October 22, 2001, the compound of Example 1 of the subject application was tested under the supervision of Dr. Ramakrishna Seethala for its activity as a modulator of the calcium sensing receptor and found to have such activity, which thereby was a reduction to practice of a species of the genus of the invention (Example 1) as claimed in Claim 1 of the subject application.

8. That prior to October 22, 2001, experiments were carried out by Ying Chen under the supervision of Timur Gungor to prepare compounds covered by the claims of the subject application, including the compound of Example 1 which experiments were recorded in Bristol-Myers Squibb Notebook No. 48255 cover page (ATTACHMENT C) and pages 101, 102, 103, 104, 105 and 108, copies of which pages are attached hereto and identified as ATTACHMENTS D, E, F, G, H and I, respectively.

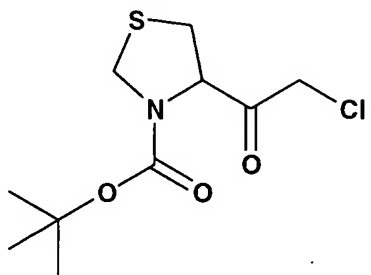
9. On Notebook page 48255-101 (hereinafter page 101) (ATTACHMENT D), entitled Proj. No. 08001, Ying Chen recorded the preparation of intermediate



from Boc-D-thiazolidine-4-carboxylic acid, which experiment he carried out prior to October 22, 2001.

Page 101 was signed by Ying Chen and witnessed by Hao Zhang, prior to October 22, 2001.

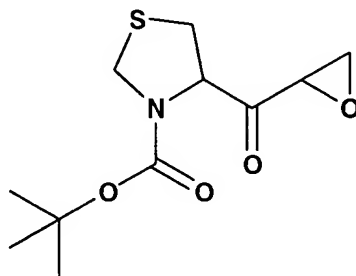
10. On Notebook page 48255-102 (hereinafter page 102) (ATTACHMENT E), entitled Proj. No. 08001, Ying Chen recorded the preparation of the chloride intermediate



prepared from the intermediate prepared as recorded on page 101 (ATTACHMENT D), which experiment was carried out prior to October 22, 2001.

Page 102 was signed by Ying Chen and witnessed by Hao Zhang, prior to October 22, 2001.

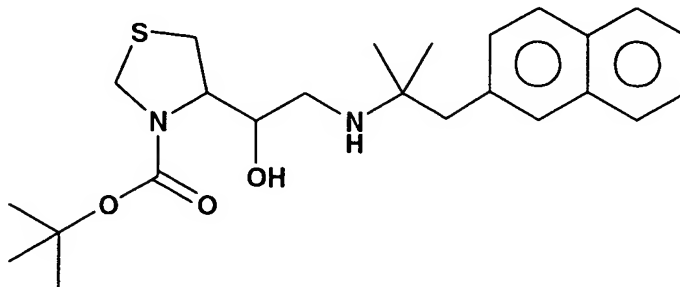
11. On Notebook page 48255-103 (hereinafter page 103) (ATTACHMENT F), entitled Proj. No. 08001, Ying Chen recorded the preparation of the intermediate



prepared from the chloride intermediate prepared as recorded on page 102 (ATTACHMENT E), which experiment was carried out prior to October 22, 2001.

Page 103 was signed by Ying Chen and witnessed by Hao Zhang, prior to October 22, 2001.

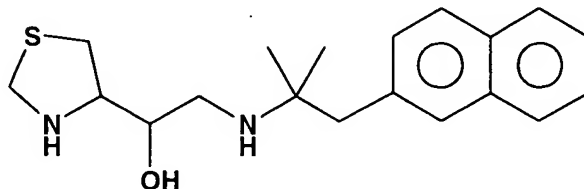
12. On Notebook page 48255-104 (hereinafter page 104) (ATTACHMENT G), entitled Proj. No. 08001, Ying Chen recorded the preparation of the intermediate



prepared from the intermediate prepared as recorded on page 103 (ATTACHMENT F), which experiment was carried out prior to October 22, 2001.

Page 104 was signed by Ying Chen and witnessed by Hao Zhang, prior to October 22, 2001.

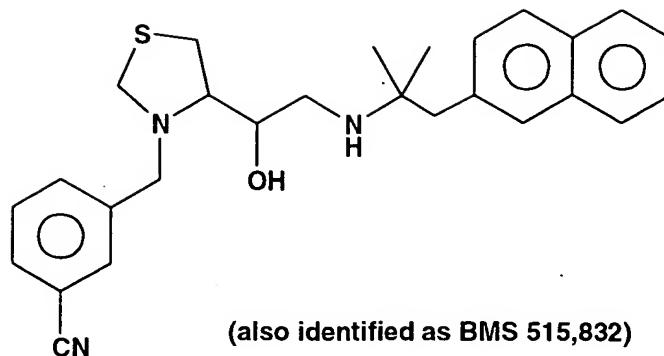
13. On Notebook page 48255-105 (hereinafter page 105) (ATTACHMENT H), entitled Proj. No. 08001, Ying Chen recorded the preparation of the intermediate



prepared from the intermediate prepared as recorded on page 104 (ATTACHMENT G), which experiment was carried out prior to October 22, 2001.

Page 105 was signed by Ying Chen and witnessed by Hao Zhang, prior to October 22, 2001.

14. On Notebook page 48255-108 (hereinafter page 108) (ATTACHMENT I'), entitled Proj. No. 08001, Ying Chen recorded the preparation of the compound of Example 1 of the subject application



prepared from the intermediate prepared as recorded on page 105 (ATTACHMENT H), which experiment was carried out prior to October 22, 2001.

Page 108 was signed by Ying Chen and witnessed by Hao Zhang, prior to October 22, 2001 (ATTACHMENT I').

15. That prior to October 22, 2001, a sample of the compound of Example 1 (BMS 515,832) of the subject application was sent to the Department of Pharmacology to Dr. Ramakrishna Seethala for testing of such compound as a modulator of the calcium sensing receptor as indicated by the compound registration paper (ATTACHMENT J).

16. In Notebook No. 49,513, pages 079 to 081, 083 and 084(ATTACHMENTS K through Q), entitled CaR response in TT cells (Table of Contents), Zhengping Ma, under the supervision of Dr. Ramakrishna Seethala, recorded experiments concerning the testing of the compound of Example 1 (referred to as BMS 515,832) as a modulator of the calcium sensing receptor.

Notebook No. 49,513, pages 079 to 081, 083 and 084 were signed by Zhengping Ma and witnessed by Yong Quan prior to October 22, 2001.

17. The testing of the compound of Example 1 for its activity in modulating the calcium sensing receptor was carried out employing the following procedure:

Calcium Receptor Inhibitor Assay Methods:

Inhibition of intracellular calcium:

Calcilytic activity was measured in human TT cells (ATCC No. CRL-1083) by determining the IC₅₀ of the test compound for blocking increases in intracellular Ca²⁺ by extracellular Ca²⁺ (as agonist of the receptor). Intracellular Ca²⁺ was measured using Fluo3,AM (Molecular probes, # F-1242) as indicator dye. Intracellular Ca²⁺ increase was measured with extracellular Ca²⁺ from 0.5 to 5 mM in Fluorescence Imaging Plate Reader (FLIPR) (Molecular Devices).

The Ca²⁺ receptor inhibitor assay procedure is as follows: TT cells were maintained in T-150 flasks in cell growth medium (F-12K Nutrition Media (Gibco 211270-022) with 10% heat inactivated FBS, and 1x Glutamax) in 5% CO₂:95% air at 37°C to 90% confluency. The medium was removed, the cell monolayer was washed with phosphate buffered saline (PBS), incubated with 0.05% trypsin at 37°C for 2 minutes and the cells were dispensed by agitation. Cells from 2 flasks were pooled and centrifuged (200xg). The cell pellet was suspended in cell growth medium. Cells were plated 30,000 cells/well for 2 days, or 24,000 cells/well for 3 days in 96-well black view plates (Falcon, VWR#624-06-468) and incubated in 5% CO₂:95% air at 37°C. Cell medium was aspirated, and cells were loaded with Fluo3 (Molecular Probes, 50 µg dissolved in 25 µl DMSO, 50 µl 20% Pluronic Acid) in base buffer (10 mM HEPES buffer containing 1x Hank's salt, 0.1% BSA, 0.05% D-glucose, 0.8 mM CaCl₂) or 1 hour in a 37°C incubator. After incubation, loading buffer was aspirated and 120 µl/well base buffer was added.

Drug plates were prepared in base buffer and loaded into FLIPR. 30 µl from drug plate was added to the cell assay plate and fluorescence signals were read in FLIPR. Drug plate was replaced with CaCl₂ plate in FLIPR plate draw and 30 µl CaCl₂ (1.7 mM final for IC₅₀s, or 2.0 mM for screening) was added into cell plate by FLIPR. The fluorescence signal was measured by reading at 1 second intervals for 30 seconds and at 3 second intervals for the next 150 seconds. Calcilytic activity of the compounds was measured by their ability to block, in a concentration dependent manner (half-log concentrations in triplicate), the intracellular Ca²⁺ level by extracellular 1.7 mM Ca²⁺. The data was processed by ActivityBase (IDDBS) and the IC₅₀ values are determined by protocols developed.

18. A summary of the test results obtained by Zhengping Ma, prior to October 22, 2001 and recorded in Notebook No. 49,513, pages 079 to 081 ,083 and 084 prior to October 22, 2001,

working under the supervision of Dr. Ramakrishna Seethala, is set out in a summary sheet (ATTACHMENT R) prepared subsequent to October 22, 2001.

19. The actual dates of Experiments regarding the preparation of the Example 1 compound recorded in Notebook No. 48255-101, 102, 103, 104, 105, 108 were carried out and the dates of signing by Ying Chen and witnessing by Hao Zhang, were all prior to October 22, 2001, but have been obliterated.

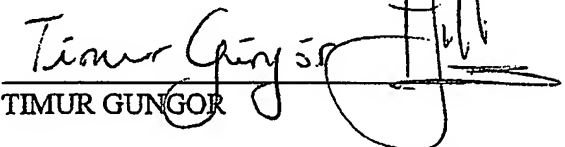
20. The actual dates of Experiments regarding the testing of the Example 1 compound recorded in Notebook No. 49,513 were carried out and the dates of signing by Zhengping Ma and witnessing by Yong Quan, were all prior to October 22, 2001, but have been obliterated.

21. The above clearly establishes conception and reduction to practice of the invention covered by the relevant claims of the subject patent application (vis-à-vis U.S. Patent No. 6,673,821) prior to October 22, 2001.

22. This Declaration is submitted prior to Final Rejection.

23. The undersigned declares further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 10/775,742 or any patent issued thereon.

Date: 03/20/06


TIMUR GUNGOR

Date: 09/26/06


JOHN K. DICKSON, JR.



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231



700098379A

JULY 14, 2004

PTAS

BRISTOL-MYERS SQUIBB COMPANY
STEPHEN B. DAVIS
PATENT DEPARTMENT
P.O. BOX 4000
PRINCETON, NJ 08543-4000

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 07/13/2004

REEL/FRAME: 014844/0440

NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

GUNGOR, TIMUR


DOC DATE: 03/23/2004

ASSIGNOR:

DICKSON, JOHN R., JR.

DOC DATE: 03/15/2004

ASSIGNEE:


BRISTOL-MYERS SQUIBB COMPANY
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000

SERIAL NUMBER: 10775742

FILING DATE:

PATENT NUMBER:

ISSUE DATE:

TITLE: NOVEL THIAZOLIDINE COMPOUNDS AS CALCIUM SENSING RECEPTOR MODULATORS

ATTACHMENT I

014844/0440 PAGE 2

SHARON LATIMER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

ASSIGNMENT

We,

Timur Gungor residing at 33 Chicory Lane
Pennington, New Jersey 08534
United States of America

John K. Dickson, Jr. residing at 2324 Walden Creek Drive
Apex, North Carolina 27523
United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

Novel Thiazolidine Compounds as Calcium Sensing Receptor Modulators

invented by us and described in the non-provisional United States patent application

Application No. 10/775,742, filed February 10, 2004,

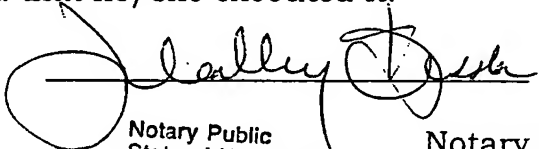
including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

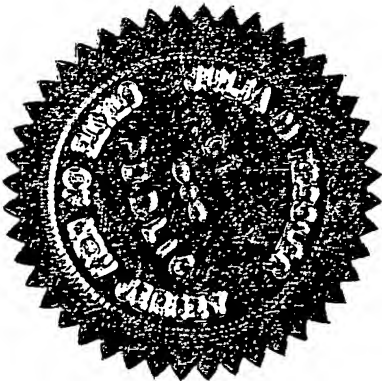
And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

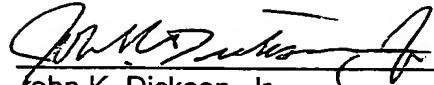
Signed this 23rd day of March, 2004 by Timur Gungor
Timur Gungor

STATE OF New Jersey)
COUNTY OF Merica) ss.

On the 23 day of March, 2004, before me came Timur Gungor, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.


Notary Public
State of New Jersey
Julia Mary Kessler
My Commission Expires
December 20, 2008
Notary Public



Signed this 15th day of March, 2004 by 
John K. Dickson, Jr.

STATE OF North Carolina)
) ss.
COUNTY OF Wake)

On the 15th day of March, 2004, before me came John K. Dickson Jr., to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.



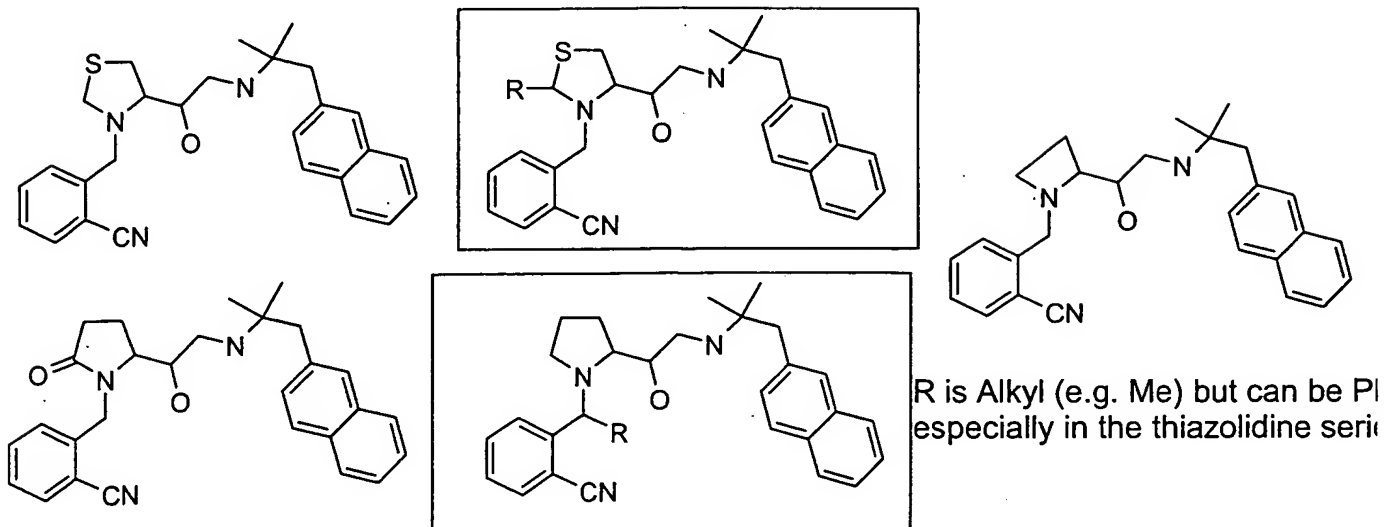
[SEAL]

Notary Public

my commission expires
12/25/2006

CaR PROGRAM TG Propositions

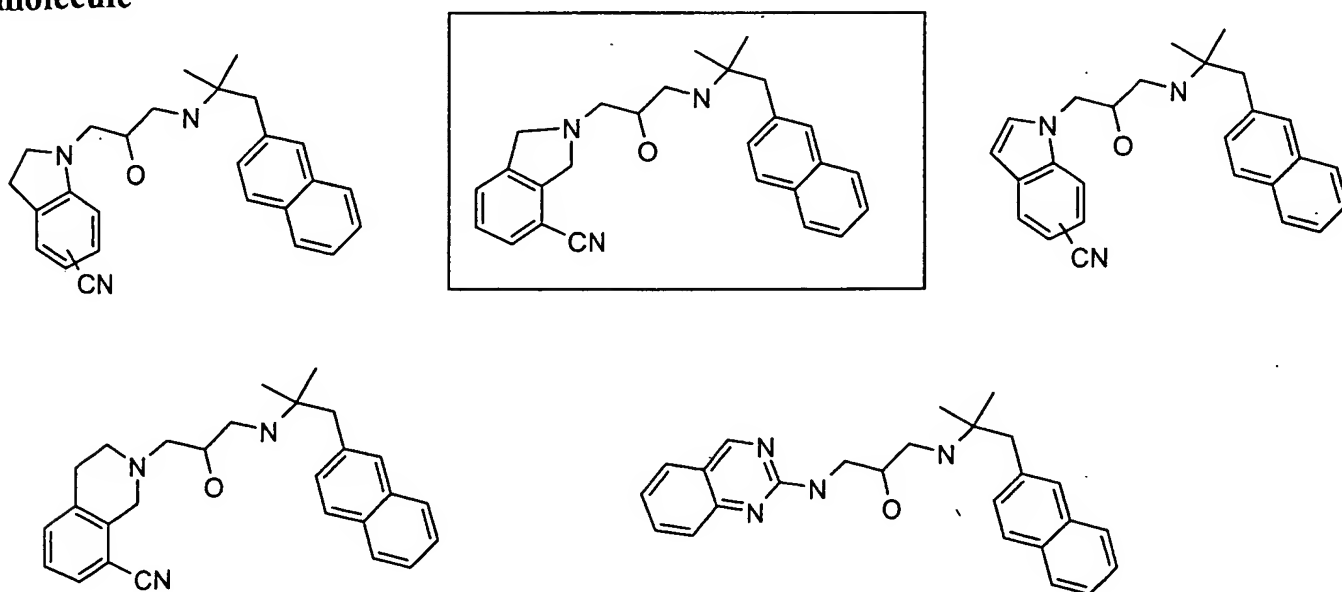
IDEAS WHITIN THE BOX:



IDEAS OUT OF THE BOX:

- 1) **Observation:** The phenyl of the Benzyl substituent is not fitting as good as it should be.

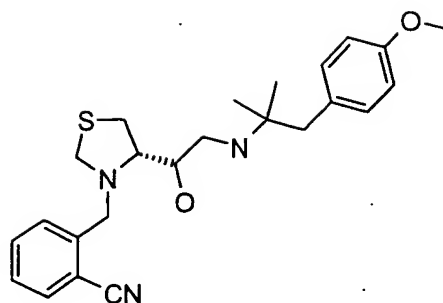
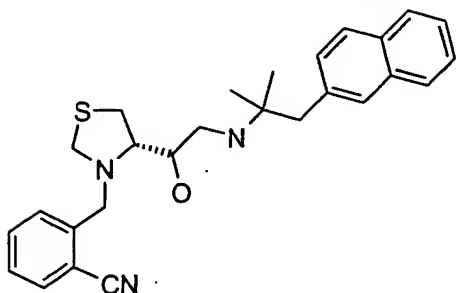
IDEA: Compounds with constrained phenyl ring in this part of the molecule



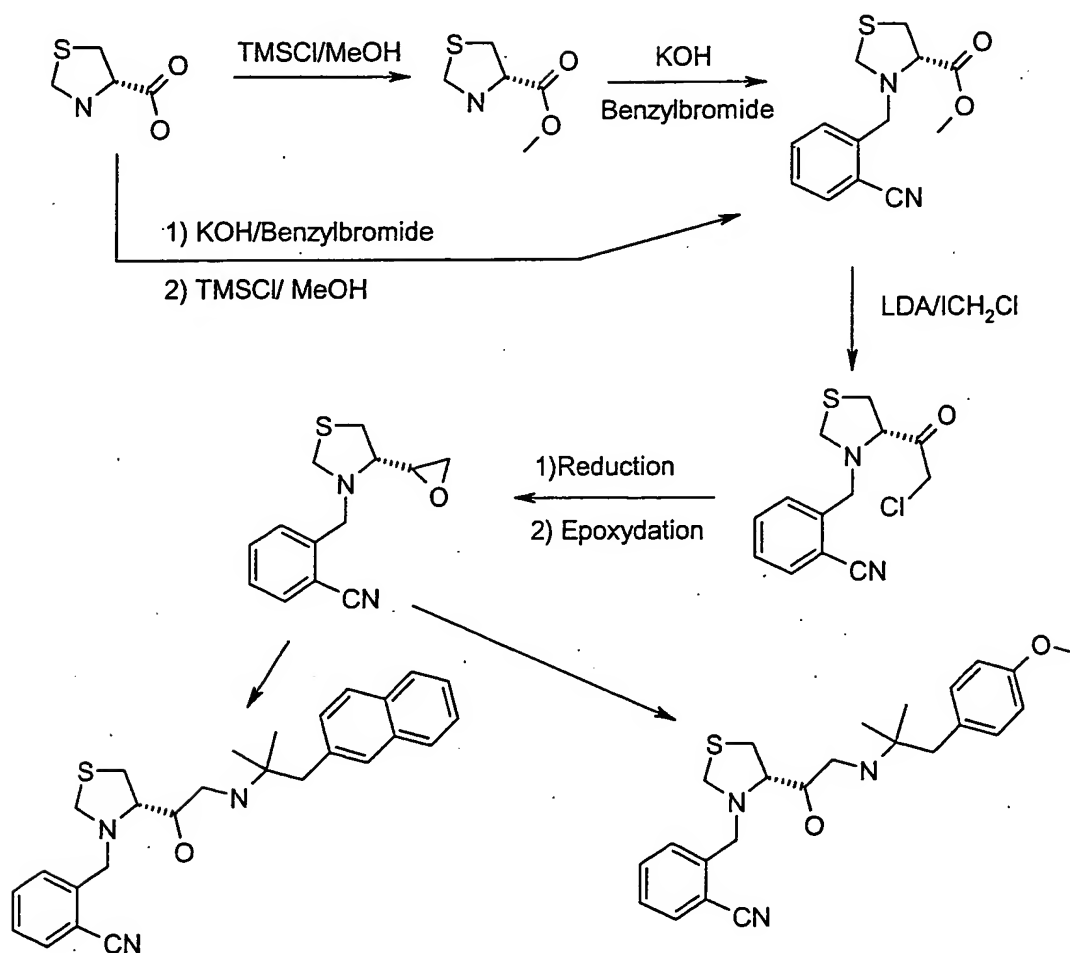
ATTACHMENT A

CaR Target

Prepare ~ 50mg of these compounds:



The reaction scheme could be the following:



The conditions for each step, by default, are those used for Proline series. Meta CN and/ or differently substituted benzylenes are to be considered according to the SAR on the Proline series.

Other modifications on the Thiazolidine ring will be made after the biology results for this two compounds.

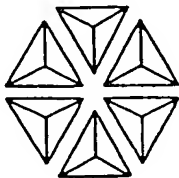
Ref: Tetrahedron Asymmetry 9 (1998) 4249-4252

J. Org. Chem. Vol. 62 No 14 (1997) p. 4770-4779

Tet.Let. Vol. 38 No 18 (1997) p. 3175-3178

ATTACHMENT B

PROPERTY OF
BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE



BRISTOL-MYERS SQUIBB

NOTEBOOK No. 48255

Assigned to Ying Chen

Subject _____

Department Name _____

Department Number _____

Date Assigned 7-6

Date Completed _____

Pages Completed from _____ to _____

Continued from Notebook Number _____

Continued in Notebook Number _____

This notebook cannot be transferred to another person

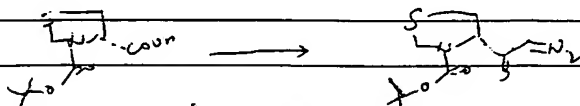
ATTACHMENT C

DATE: _____

PROJ. NO. 2817

EXPT. NO. _____

SUBJECT _____



5

Boc-D-thiazolidine 5.0 g 21.4 mmol

-4-carboxylic acid

isobutylchloroformate 2.76 ml 21.4 mmol

Et₃N 3.0 ml 21.4 mmol

THF 50 ml

MWDG 11.7 g

10

KOH/H₂O 158 in 37 mlEt₂O 125 ml

To a two phase solution of KOH and Et₂O at 0°C was added MWDG portionly. The ether layer was decanted to a flask.

15

The fresh made CH₂ in Et₂O was kept at 0°C.

To a solution of Boc-D-thiazolidine-4-carboxylic acid, Et₃N in THF at -10°C (acetone + ice) was added dropwise isobutylchloroformate. The reaction was kept at -10°C for 30 min then filtered (white solid was resulted from Et₃N.HCl). The filtrate was stirred at -10°C. A solution of CH₂ in Et₂O was added. Stirring was continued for 1h. then poured to RT.

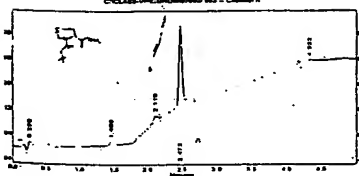
20

Et₂O was added and the solution washed with H₂O, satd NaHCO₃ brine and dried over MgSO₄. Evaporation gave a yellow oil. Purification was performed by flash column on silica gel, loaded with CH₂Cl₂. Eluted with 25% Et₂O in hexane. Pure fractions were combined and evaporated to give a pale yellow oil.

25

C:\CLASS\BRI\BRI\48255-101\50_003

Instrument = HP-1027-LSMS1
Well = 182 Inj. Vol. = 10 ul
Start 1 = 0
Final 1 = 100
Gradient Time = 4 min
Flow Rate = 4 ml/min
Wavelength = 220
Solvent A = 10% MeOH - 90% H₂O - 0.34 TFA
Solvent B = 90% MeOH - 10% H₂O - 0.18 TFA
Column 2: Phenomenex ODS 4.6 x 50 mm (4 min)
48255-101



RT	Area	Area %	Placed
6.76	21325	2.367	181
7.47	27489	2.944	2134
2.12	15642	6.886	7375
2.07	458277	49.802	12172
4.33	35915	38.662	9

~~48255-101-27~~ 48255-101-27 4.44 g (80.7%)

¹H NMR (CDCl₃, 400 MHz) was consistent
¹³C NMR

LC-MS M+23 = 280

RQ 22912 for MS M+1 = 258

OK

SIGNED

DATE

WITNESSED AND UNDERSTOOD BY

DATE

CROSS REFERENCES:

ATTACHMENT D

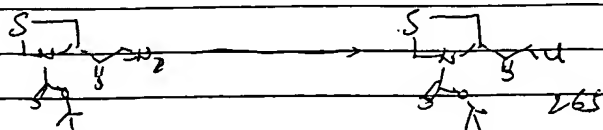
DATE: ____

PROJ. NO.

08001

EXPT. NO.

SUBJECT



5	4825J-701-2f	44 g
	HCl (4N)	5 ml
	CH ₂ Cl ₂	10 ml

To a solution of 48255-101-27 in CH₂Cl₂ at -10°C, a solution of 48114 in dihex was added dropwise. (A lot of bubbles). The reaction was stirred at -10°C for 30 min. Hex was evaporated by a vacuum pump without heating. The rest of solution was warmed to RT. Evaporation was without heat to give a yellow oil. 4.4g

18255-0248

15 CC-MS $M + 23 = 188$
HNMR were consistent
13C NMR

RQ 22935. 7K2723f M-1 = 263.9

20

25

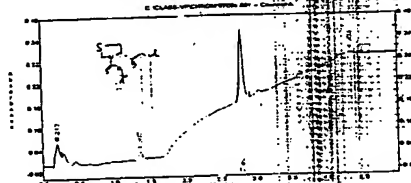
	R_1			Elect/Hor
	C			$= 1:1$
	SM			

30

File

: C:\CLASIF-VP\CHK24.97030.001

Instrument = HPW-1166-LCMS1
Well = 102 Inj. Vol = 100 µl
Start = 8 = 0
Final 1 = 8 = 100
Gradient Time = 4 min
Flow Rate = 1 ml/min
Wavelength = 220
Solvent A = 10% MeOH - 90% H2O - 1.175
Solvent B = 90% MeOH - 10% H2O - 1.175
Column 1 = Phenomena Luna C18 4.6mm x 150mm 5µm gradient



Channel A Results

Peak	PT	Area	Area %	Label
1	0.21	68845	1.27	B
2	1.37	34291	0.63	2223
3	2.81	969750	17.92	4413
4	6.75	176176	3.24	400
Totals:		1262062	100.00	

SIGNED

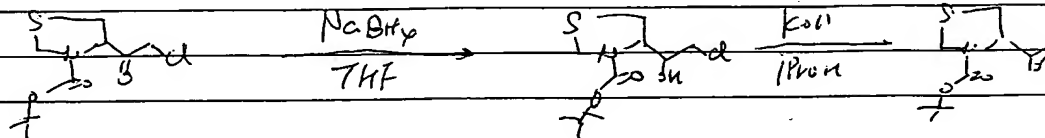
DATE

WITNESSED AND
UNDERSTOOD BY:

CROSS REFERENCES:

ATTACHMENT E

DATE: _____ PROJ. NO. 0801 EXPT. NO. _____
SUBJECT: _____



5 48255-102-14 4.4 g 16.6 mmol
NaBH₄ 614 mg 16.6 mmol
THF 30 ml

10 To a solution of 48255-102-14 in THF at RT was added NaBH₄. The reaction was stirred at RT for 30 min. LC-MS showed 2 SM left. H₂O was added to quench the reaction. EtOAc was added and the solution was washed with sat'd NaHCO₃, brine and dried over MgSO₄. Evaporation gave a crude oil. 48255-103-13

LC-MS showed right M+23 = 290 two isomer ratio 3:1

15 To a solution of 48255-103-13 in iPrOH (10 ml) was added KOH (10 ml). The mixture was stirred at RT for 1 h. EtOAc was added and the organic layer was washed with sat'd NaHCO₃, brine and dried over MgSO₄. Evaporation gave a crude oil. 48255-103-18

¹H NMR showed the isomer ratio = 2:1

20 Purification was performed by flash chromatography on silica gel, loaded with crude, eluted with 8% EtOAc in hex. Pure fractions were combined and evaporated to give a crude oil 48

Isomer I 48255-103-23 1.2 g

¹H NMR and ¹³C NMR were consistent.

25 IR 2350, 1727 cm⁻¹ MS: M+1 = 232.

Isomer II 48255-103-27 1.6 g

IR 2305

IR 2770 M+1 = 232

SIGNED

DATE

WITNESSED AND UNDERSTOOD BY:

DATE

CROSS REFERENCES:

ATTACHMENT F

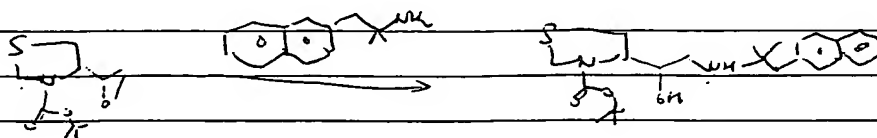
DATE: _____

PROJ. NO. _____

08007

EXPT. NO. _____

SUBJECT _____



5 48255-103-23 500 mg 2.17 mmol
 amine 432 mg 2.17 mmol

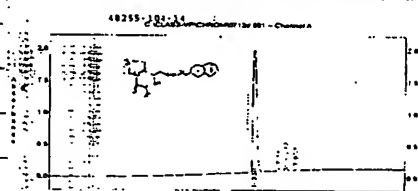
The mixture of 48255-103-23 and amine was heated together at 80°C for 3 hr. TLC and LC-MS showed no epoxide left. The reaction was cooled to RT. Purification was performed by flash chromatography on silica gel, loaded with crude, eluted with 3% methanol in CH₂Cl₂ + 0.1% NH₄OH. Pure fractions were combined and evaporated to give a colorless oil.

48255-100-18 833 mg (89%)
 RQ 23057 BMS-538174-01

15 MS (TR 273.84) m+1 = 431

1H NMR new consistent
 13C NMR

Analytical HPLC Report
 File: C:\CLASS\VP\KROB\07120.001
 7/24/01
 Instrument: HPLC-L132-HPLC
 Well: 177 Inj. Vol.: 10 uL
 Start & B: 0
 Final & B: 100
 Gradient Time: 8 min
 Flow Rate: 2.5 ml/min
 Wavelength: 220
 Solvent A: 10% MeOH - 90% H₂O - 0.2% H₃PO₄
 Solvent B: 90% MeOH - 10% H₂O - 0.2% H₃PO₄
 Column 1: Zorbax SB-C18 4.6mm ID x 75mm (8 HPLC)



Peak	RT	Area	Area %	Placed
1	4.23	7623776	96.697	16497
2	7.31	76189	0.002	95302
3	7.33	152878	0.002	96789
4	7.44	31242	0.004	71777
Total		7863122	100.000	

35

SIGNED _____

DATE 1-1

WITNESSED AND UNDERSTOOD BY: _____

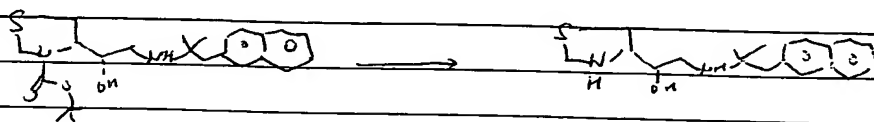
CROSS REFERENCES:

ATTACHMENT G

DO NOT WRITE IN THIS MARGIN

DATE: _____ PROJ. NO. 08007 EXPT. NO. _____

SUBJECT _____

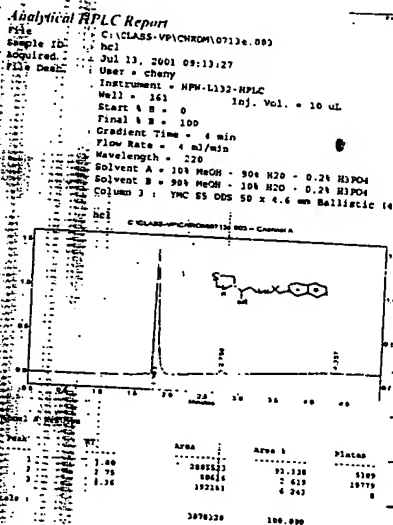


5
 48255-104-14 803 mg
 HCl in dioxane 20 ml
 THF 10 ml

10
 To a solution of 48255-104-14 in THF at RT ~~was~~ added 4N HCl in dioxane. The reaction was stirred at RT for 24 hr. Then evaporated to dryness. The residue was dissolved in sat'd NaHCO₃, EtOH was added and the organic layer was washed with brine and dried over MgSO₄. Evaporation gave a pale-yellow oil.

48255-105-14

15
¹H NMR ¹³C NMR were consistent, RQ



SIGNED

DATE

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CROSS REFERENCES:

ATTACHMENT H

DO NOT WRITE IN THIS MARGIN

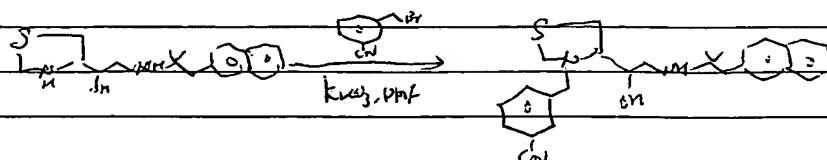
DATE:

PROJ. NO.

08 Oct 7

EXPT. NO.

SUBJECT



5	48255-105-14	100 mg	0.3 mmol
	2-bromotoluene	60 mg	0.3 mmol
	K ₂ CO ₃	46 mg	0.3 mmol
	DMF	2 ml	

DO NOT WRITE IN THIS MARGIN

- 10 The mixture of 48255-105-14, 2-bromotoluene and K₂CO₃ in DMF was stirred at 40°C for 5 hr, then cooled to RT, stirring was continued overnight (3 days). Et₂O was added to the reaction and the solution was washed with H₂O (two times), brine and dried over MgSO₄. Purification was performed by flash chromatography on silica gel, loaded with CMC, eluted with 8% CH₂Cl₂ in CHCl₃ with 0.2% NH₄OH. Pure fractions were combined and evaporated to give a white foam.
- 15 HPLC showed small impurities. Purified again by flash column, loaded with CMC, eluted with 12% CH₂Cl₂ in Et₂O. Pure fractions were combined and evaporated to give a foam.

- 20 48255-108-1a
48255-108-1a was dissolved in CH₂Cl₂. HCl in Et₂O (in 1 ml) was added. The mixture was stirred at RT for 30 min then evaporated to dryness. 120 mg
48255-108-2a

- 25 RQ 23486
MS (Molecular)
MS (Atomic)
EA
OR
PKC
- 30
- 35

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DATE -

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DATE

CROSS REFERENCES:

ATTACHMENT I

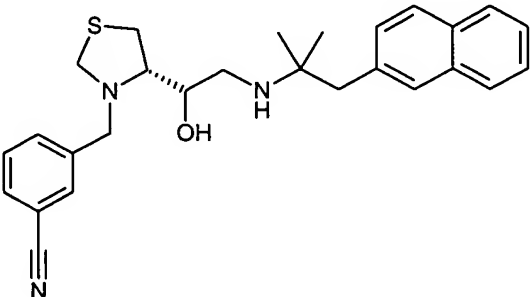
2D	3D	Biology	CTR	HTS	Inventory	Library	Program	Property	Reaction	Reagent	Select	Info
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COMPOUND REGISTRATION
PROPRIETARY - CONFIDENTIAL

PART 1 - Registry Office Use

BMS # ASSIGNMENT DATE	Checked/Approved DATE	THERAPEUTIC AREA	LOT	BMS NUMBER - FORM
		MD	002	BMS-515832 - 02

PART 2 - Completed by the Submitter

STRUCTURE <input checked="" type="checkbox"/> FINAL PRODUCT <input type="checkbox"/> INTERMEDIATE PRODUCT <input checked="" type="checkbox"/> HOMOCHIRAL <input type="checkbox"/> RACEMATE <input type="checkbox"/> DIASTEREOMER MIXTURE		SUBMITTER NAME / PHONE Chen, Ying / 5588 SOURCE / LOCATION BMS / HW																																																	
		PROJECT NUMBER 08007 LIBRARY REFERENCE 48255-108-20 ALLIANCE ID Start Date End Date Contact																																																	
MOL NAME isomer B CHEMICAL NAME SALT FORM 2.00 hydrochloride		MOLECULAR FORMULA $C_{27}H_{31}N_3O_3S$ Molecular Weight 445.63 Formula Weight 518.55																																																	
<table border="1"> <thead> <tr> <th colspan="2">ANALYTICAL TESTS</th> <th colspan="2">ELEMENTAL ANALYSIS</th> <th colspan="2">SOLVATES</th> </tr> <tr> <th>sequence #:</th> <th></th> <th>% calc</th> <th>% found</th> <th>solvent</th> <th>ratio</th> </tr> </thead> <tbody> <tr> <td>Elem Anal</td> <td>RQ23496</td> <td>C = 62.54%</td> <td></td> <td></td> <td></td> </tr> <tr> <td>MS Low Res</td> <td></td> <td>H = 6.41%</td> <td></td> <td></td> <td></td> </tr> <tr> <td>MS High Res</td> <td></td> <td>N = 8.10%</td> <td></td> <td></td> <td></td> </tr> <tr> <td>NMR Carbon</td> <td></td> <td>O = 3.09%</td> <td></td> <td></td> <td></td> </tr> <tr> <td>NMR Proton</td> <td></td> <td>S = 6.18%</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Rotation</td> <td></td> <td>Cl = 13.67%</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>		ANALYTICAL TESTS		ELEMENTAL ANALYSIS		SOLVATES		sequence #:		% calc	% found	solvent	ratio	Elem Anal	RQ23496	C = 62.54%				MS Low Res		H = 6.41%				MS High Res		N = 8.10%				NMR Carbon		O = 3.09%				NMR Proton		S = 6.18%				Rotation		Cl = 13.67%				APPEARANCE off-white powder TOTAL AMOUNT (MG) 82.0 MP or BP (°C) Decomposes % PURITY % ACTIVE 98.1 85.94	
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COMMENTS

HPLC purity = 98.1% (220 nM), Rt = 6.01 min; Zorbax SB C18 4.6 x 7.5 mm; 50-100% B:A
 (A = 90% H₂O/CH₃OH + 0.2% H₃PO₄; B = 90% CH₃OH/H₂O + 0.2% H₃PO₄); linear gradient over 8 minutes, then 100% B; flow rate = 2.5 ml/min.

BRISTOL-MYERS SQUIBB

NOTEBOOK No. 49513

Assigned to

Zhenyong Ma

Subject

Department Name

Aging Research

Department Number

800 1602

Date Assigned

Date Completed

Pages Completed from

821

to

250

Continued from Notebook Number

49423

Continued in Notebook Number

51731

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49513

TABLE OF CONTENTS

PROJECT OR EXPERIMENT NO.	PRODUCT OR SUBSTANCE	STUDY PERFORMED OR OBJECTIVE	PAGES
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IC50s: BMS-515832-02-002, 280429, 280587

CaRi response in TT cells

49513-079
49513-088

49513 079

NOTEBOOK No. PAGE

CaR response in T1 cells

T1 cells plated on _____ at 24,000 cells/well used (see also 49513-068)
0.8 mM Ca^{2+} basal, 1.7 mM Ca^{2+} stimulation.
See also 44676-072 for basic protocol

Plate 1

BMS-515832-02-002 (μM) (A1:C6)

synthesis

	1	2	3	4	5	6
A	1.0000	0.3333	0.1111	0.0370	0.0123	0.0041
B	1.0000	0.3333	0.1111	0.0370	0.0123	0.0041
C	1.0000	0.3333	0.1111	0.0370	0.0123	0.0041

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513 081

NOTEBOOK No.

PAGE

Signal Test

Continued

SIL

Plate 1 ZMCA072601a_n0

Minimum 9045.6 16.47%

Maximum 12823.2

Average 10829.4

STDEV 738.3

	1	2	3	4	5	6
A	11194.4	10826.4	10314.4	10444.0	10192.8	9940.0
B	10764.0	11074.4	10508.0	9893.6	9832.8	9298.4
C	9922.4	11116.0	10592.8	10845.6	10831.2	10120.8

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13543 03

NOTEBOOK No. PAGE

Continued

ZnCo072501a_n1.fid



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Range = (-1000,19000)

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49513 083

NOTEBOOK No. PAGE

Continued

File = D:\mzh\ZMC072501a_n1.fid

Plate 1

Statistic = Max - Min

Start Sample = 11

End Sample = 45

Positive Scaling = On

Negative Correction = Off

Bias Value Subtract = On

Spatial Uniformity Correction = On

Bias Sample = 1

	A	B	C	D	E	F	G	H
1	3.79	4.98	2.39	43.82	15.29	26.01	2.4	3.96
2	4.58	4.47	3.85	60.51	45.13	65.27	4.92	3.28
3	11.06	12.77	17.3	95.26	62.57	82.4	20.93	11.91

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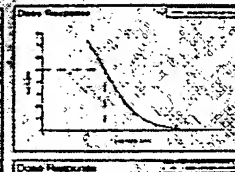
NOTEBOOK No. PAGE

Continued

Test Occasion ID:
Protocol ID:
Study ID:
User ID:MDCaR010726-1
CaR_HJC58
CaR
Zhengping Ma

Plate 1

Compound ID	Conc (µM)	% TL1	% TL2	% TL3	Average % TL	StDev	PGSD
BMS-515632-02-002	1.000	3.79	4.89	2.39	3.72	1.30	0.024921
	0.333	4.56	4.47	3.85	4.29	0.39	0.0115
	0.111	11.06	12.77	17.3	13.71	3.22	-1.15
	0.037	32.3	43.99	44.12	40.14	6.79	
	0.012	56.51	48.98	99.99	68.53	27.51	
	0.004	41.18	61.95	37.58	46.90	13.15	



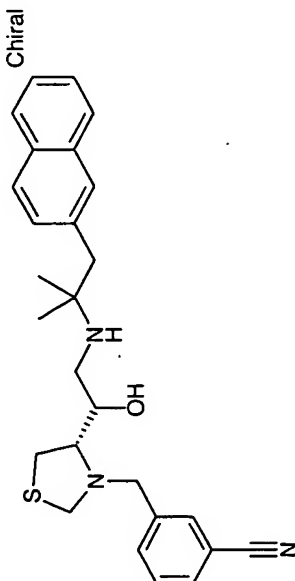
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Zhengping Ma

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2D	3D	Biology	CTR	HTS	Inventry	Library	Program	Property	Reaction	Reagent	Select	Info																																																																																																												
<div><div></div><div><table><tr><td colspan="2">BMS #</td><td colspan="2">BMS-515832</td><td colspan="2">Form</td><td colspan="2">Lot</td><td colspan="2">Molecular Wt</td><td colspan="2">Formula Wt</td></tr><tr><td colspan="2">Formula</td><td colspan="2">C₂₇ H₃₁ N₃ O S</td><td colspan="2">Appearance</td><td colspan="2">002</td><td colspan="2">445.63</td><td colspan="2">518.55</td></tr><tr><td colspan="2">Submitter</td><td colspan="2">Chen, Ying</td><td colspan="2">Chemist's Notebook</td><td colspan="2">off-white powder</td><td colspan="2">Location</td><td colspan="2">Project #</td></tr><tr><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2">48255-108-20</td><td colspan="2">Amount (MG)</td><td colspan="2">Purity</td></tr><tr><td colspan="2">Date</td><td colspan="2"></td><td colspan="2">Molname</td><td colspan="2">isomer B</td><td colspan="2">82.0</td><td colspan="2">98.1</td></tr><tr><td colspan="2">Protocol</td><td colspan="2">CaR_H_IC50</td><td colspan="2">Version</td><td colspan="2">Biologist</td><td colspan="2">Biologist's Notebook</td><td colspan="2"></td></tr><tr><td colspan="2"></td><td colspan="2"></td><td colspan="2">1</td><td colspan="2">MAZH</td><td colspan="2"></td><td colspan="2"></td></tr><tr><td colspan="2">Protocol Name</td><td colspan="2">Ca+ Sensitive Receptor, Human species, Dose Response assay</td><td colspan="2">Protocol User Group</td><td colspan="2">MD_PPAR</td><td colspan="2">PWG List Name</td><td colspan="2"></td></tr><tr><td colspan="2">Parameter</td><td colspan="2">RECEPTOR SPECIES</td><td colspan="2">Assoc Value</td><td colspan="2">Ca SENSITIVE HUMAN</td><td colspan="2">Result Comments</td><td colspan="2"></td></tr></table></div></div>													BMS #		BMS-515832		Form		Lot		Molecular Wt		Formula Wt		Formula		C ₂₇ H ₃₁ N ₃ O S		Appearance		002		445.63		518.55		Submitter		Chen, Ying		Chemist's Notebook		off-white powder		Location		Project #								48255-108-20		Amount (MG)		Purity		Date				Molname		isomer B		82.0		98.1		Protocol		CaR_H_IC50		Version		Biologist		Biologist's Notebook								1		MAZH						Protocol Name		Ca+ Sensitive Receptor, Human species, Dose Response assay		Protocol User Group		MD_PPAR		PWG List Name				Parameter		RECEPTOR SPECIES		Assoc Value		Ca SENSITIVE HUMAN		Result Comments			
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Library Name	Test Occasion	Test Occasion Notes	Parent_Study
Alliance ID	MDCaR010726-1		
	MDCaR010726-1		
	MDCaR010726-1		
	MDCaR010809		
	MDCaR010816		

Condition 1	Condition 2	Condition 3	Condition 4	Name	NValue	Units

Study	Protocol	V	Type	AValue	< / >	NValue	Units	C	C 1 AValue	C 2 AValue	C 3 AValue	C 4 AValue	Date
CaR	CaR_H_IC50	1	HILL	-1.15		-1.1500							
CaR	CaR_H_IC50	1	IC50	0.024921		0.0249	uM						
CaR	CaR_H_IC50	1	P CONTROL	4.29		4.2900			0.33				

ATTACHMENT R

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